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Overcoming resistance in glioblastoma immunotherapy: lessons from the past and opportunities for the future

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Abstract

Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, characterized by rapid proliferation, diffuse invasion, and profound therapeutic resistance, leading to a median survival of approximately 15 months despite maximal treatment. Immunotherapy, which has transformed outcomes in other malignancies, has shown limited success in GBM due to its immune-privileged environment, extensive immunosuppressive networks, and tumor heterogeneity. Clinical trials of checkpoint inhibitors, cancer vaccines, CAR-T cells, oncolytic viruses, and microenvironment-targeting agents have largely failed to produce durable survival benefits, often hindered by poor T-cell infiltration, antigen loss, and redundant suppressive mechanisms within the tumor microenvironment. Lessons from these failures highlight the necessity of mechanism-informed strategies that address the tumor's immune evasion. Next-generation approaches emphasize priming the tumor to enhance immune visibility, targeting multiple antigens to prevent escape, optimizing locoregional CAR-T delivery, using oncolytic viruses as immune catalysts rather than sole cytotoxic agents, and strategically modulating the microenvironment to support effector responses. By integrating these insights, rational combination strategies can transform GBM immunotherapy from incremental efficacy to meaningful clinical benefit. Translational rigor, adaptive trial designs, and biology-driven interventions are essential to overcoming the complex barriers posed by GBM and achieving durable anti-tumor immunity.

Keywords: CAR-T cells; Checkpoint inhibitors; Glioblastoma; Immunotherapy; Tumor microenvironment.

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